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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,493	11/21/2003	Arthur M. Krieg	C1039.70021US01	3218

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EXAMINER	
GUSSOW, ANNE	
ART UNIT	PAPER NUMBER
1643	
MAIL DATE	DELIVERY MODE
04/16/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,493	KRIEG ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-53,59-69,71-73 and 75-80* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 4, 2010 has been entered.

2. No claims have been amended, or added.

Claims 1-41, 54-58, 70 and 74 have been previously cancelled.

3. Claims 42-53, 59-69, 71-73, and 75-80 are under examination.

Rejections Maintained

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 42-53, 59-69, 71-73, and 75-80 under 35 U.S.C. 112, first paragraph, as lacking enablement is maintained.

Applicant's arguments filed February 4, 2010 have been carefully considered by the examiner but they are deemed not to be persuasive. The response states that the invention relates to the discovery that unmethylated CpG oligonucleotides can provoke an immune response, which includes the induction of interferon-γ (IFN-γ), IL-12, and IL-6, as well as NK cell activation (See e.g., page 17, lines 3-8 of the application as filed). The references previously cited by Applicant (Trinchieri et al., Brunda et al., U.S. Pat. No.: 4,883,662, and Hayashi et al.) demonstrate that at the time of filing the application, there was an art-recognized connection between the induction of these cytokines and the treatment of cancer ... Accordingly, the cited references establish that the skilled artisan would have recognized the utility of a drug which is effective in inducing IL-12, IFN-7 and NK cell activation as a compound which would be useful in the treatment of cancer ...The claims are not limited to monotherapy. The addition of other therapeutic agents is encompassed by the broadest claims. Further claims 43, 44, 68, 72-73, and 79- 80 all specifically recite the combination of a CpG ODN with a second therapeutic agent (see response pages 6-9).

Response to Arguments

Applicant's arguments are directed to the correlation between induction of cytokines and the treatment of cancer. Applicant's arguments are also directed to the claims being drawn to combination therapy with CpG oligonucleotides.

In response to these arguments, regarding the induction of cytokines, applicant's have cited a number of references drawn to the induction of cytokines, as set forth previously, none of these references speak to the treatment of cancer by administering

oligonucleotides. Applicant has not shown a correlation of a cancer specific immune response with the increase of these cytokines. Applicant's specification does of not teach treatment of any cancer in any model system by administering CpG oligonucleotides.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In deciding In re Fisher, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005 (CA FC 1997).

Supporting documents cannot be relied upon to correct the deficiencies of the specification by supplying the necessary and essential teachings, guidance, and exemplification that the specification lacks. MPEP 2164.05(a) states that if individuals of skill in the art state that a particular invention is not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993) an article published 5 years after the filing date of the application adequately supported the examiner's position that the physiological activity of certain viruses was sufficiently unpredictable so that a person skilled in the art would

not have believed that the success with one virus and one animal could be extrapolated successfully to all viruses with all living organisms. Hence, as stated in the previous office actions, the studies published well after the filing date of the instant application clearly recognize the obstacles in treating cancers comprising oligonucleotides containing an unmethylated CpG dinucleotide and address the unpredictability.

Regarding the combination therapy, the instant independent claims are not drawn to a combination therapy with CpG oligonucleotides and a second treatment. While there are dependent claims drawn to a combination therapy, the broadest claims are drawn to a single treatment regimen. Additionally, the treatment of cancer is an unpredictable event; tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack. Krieg (Journal of Investigation, 2007. as cited on the IDS filed April 22, 2009) teaches administration of CpG motifs as adjuvants to cancer vaccines and in combination with conventional chemotherapy and other therapies (abstract). Krieg teaches CpG ODN (oligonucleotides) needs to be combined with either a tumor vaccine or with other effective antitumor strategies (see page 1190 1st column and table 4). Krieg also teaches the focus of ongoing clinical trials has shifted to combination therapies (page 1190 2nd column).

Further, Forni et al (Cancer Research, 2000, 60; 2571-2575, as cited on the PTO-892 mailed April 27, 2009) disclose tumor cells have the ability to escape immune reactions and tumor masses can suppress immune attack (see page 2571, right column). Mouse models show that elicitation of a significant immune response in patients with advanced tumors is exceedingly difficult, and only a minority of tumor-

bearing mice are cured. "As a tumor increases in size, it becomes refractory to immunotherapy" (see page 2571, left column). A similar picture is emerging from Phase I immunotherapy trails where only a few patients with established tumors display objective and in any event temporary responses (see page 2571, right column). Tumor burden and antigenic drift continue to present serious burdens for successful cancer therapy in vivo. Tumors are classified as immunogenic or non-immunogenic, solid or hematological in nature. Effective cancer strategies should be designed to deal effectively with the nature of each of these classifications.

Regarding the use immunostimulatory nucleic acids, the art recognizes a number of specific characteristics of the oligonucleotide, which are critical for its function as an immunostimulatory molecule. For instance, Agarwal et al. (Trends in Mol. Med., 2002; 8:114-121, as cited on the PTO-892 mailed September 1, 2005) teaches that the pattern and kinetics of induction of the cytokines in vivo depends on the sequences flanking the CpG dinucleotide, as well as the dose, the route of administration and the host animal species (see page 16 "therapeutic potential of CpG DNA" in particular) and that there is a species-dependent selectivity of CpG DNA, and that the optimal CpG DNA sequences for many vertebrate species are not yet known (see page 119 "concluding remarks" in particular). Similarly, Crooke et al. (Therapeutic application of Nucleotides, R.G. Landers Co., Austin, TX, 1995, Chapter 5, pages 63-84, as cited on the PTO-892 mailed September 1, 2005) teach phosphorothioate nucleotides clearly have significant limits (see page 79 table 5.2, in particular): pharmacodynamically, they have relatively low affinity per nucleotide unit, pharmacokinetically, phosphorothioates

do not cross blood brain barrier, are not significantly orally bioavailable and may display dose-dependent pharmacokinetics. Toxicologically, clearly the release of cytokines, activation of complement and interference with clotting will pose dose limits if they are encountered in the clinic. All of this underscores the criticality of providing workable examples which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

Therefore after a fresh consideration of the claims and the evidence provided the rejection is maintained.

Conclusion

6. No claims are allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
April 14, 2010

/Anne M. Gussow/
Examiner, Art Unit 1643